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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/575,696	PRENTICE ET AL.	
	Examiner	Art Unit	
	JENNIFER DUNSTON	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 April 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/5/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendices I-VIII*.

DETAILED ACTION

Claims 1-30 are pending in the instant application.

Information Disclosure Statement

Receipt of an information disclosure statement, filed on 9/5/2007, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action.

Specification

The disclosure is objected to because of the following informalities: there is a typographical error at paragraph [0021]. Specifically, the abbreviation for bovine growth hormone (BGH) is misspelled as "BHG." The correct abbreviation is shown at paragraph [0024].

Appropriate correction is required.

The use of the trademark GENBANK (page 6, line 8 and page 8, line 19) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Drawings

The drawings are objected to because Figures 6 and 7 are illegible and will not reproduce well. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claim 1 is objected to because of the following informalities: the term "*dhfr*" should be spelled out at the first occurrence followed by the abbreviation in parenthesis. Claims 2-30 depend from claim 1 and are objected to for the same reason applied to claim 1. Appropriate correction is required.

Claim 2 is objected to because of the following informalities: the phrase "promoter/enhancer region" should be inserted after the parenthetical phrase hCMV IE1 to improve the grammar of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 14, 18, 22 and 29 are rejected under 35 USC § 101 because the claimed invention is directed to non-statutory subject matter. The specification teaches that the invention relates to recombination vectors and recombination cassettes, and to methods for expression of an exogenous molecule in an organism or host cell (e.g., paragraph [0001]). The specification envisions the introduction of nucleic acid molecules into target cells and tissues as a therapeutic delivery system (e.g., paragraph [0002]). The specification does not explicitly define the term "organism"; however at paragraph [0051], the specification indicates that many organisms have recA-like recombinases with strand-transfer activities, including human cells. Thus, the term "organism" is reasonably interpreted as encompassing humans. Since the specification envisions methods for delivery and expression of exogenous nucleic acid molecules in an organism (e.g., paragraphs [0001]-[0002]), the claims are reasonably interpreted as encompassing a cell that is intended to be present in an organism, including a human, in some embodiments. Thus, the cell is present or intended to be present in a human being, which is non-statutory subject matter. As such, the recitation of the limitation "isolated" would be remedial. See 1077 O.G. 24, April 21, 1987.

Claim 14 is drawn to a host cell comprising a recombination vector of claim 11. Given the broadest reasonable interpretation of the claim in light of the specification, the claim is reasonably interpreted as a host cell in a human to which the vector of claim 11 was delivered.

Claim 18 is drawn to a host cell comprising a recombination cassette of claim 1. Given the broadest reasonable interpretation of the claim in light of the specification, the claim is reasonably interpreted as a host cell in a human to which the recombination cassette of claim 1 was delivered.

Claim 22 is drawn to a recombination system comprising a recombination cassette of claim 1, and a host cell comprising a FRT site. Given the broadest reasonable interpretation of the claim in light of the specification, the claim is reasonably interpreted as a host cell in a human to which a recombination cassette comprising a FRT site was delivered.

Claim 29 is drawn to a kit comprising the vector of claim 10 and a host cell comprising a FRT site. Given the broadest reasonable interpretation of the claim in light of the specification, the claim is reasonably interpreted as a host cell in a human to which a recombination cassette comprising a FRT site was delivered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 11 and 14-21 are rejected under 35 U.S.C. 102(e) as being anticipated by DuBridge (WO 2004/029284, cited as reference AD on the IDS filed 9/5/2007; see the entire reference).

Regarding claim 1, DuBridge teaches an integration cassette for site-specific recombination comprising a promoter region, an enhancer region, a polynucleotide of interest that encodes a reporter or a desired protein product, a 3' termination sequence with a polyadenylation (polyA) signal, where the promoter/enhancer, polynucleotide of interest and 3' termination sequence are operably linked, and where the polynucleotide of interest is flanked by recombination sites (e.g., page 2, lines 27-31; page 26, line 7-21; page 27, line 11 to page 30, line 21). DuBridge teaches the cassette where the site-specific recombination sites are FRT sites (FRT recombination domains) (e.g., page 17, lines 5-9). DuBridge teaches the cassette further comprising a DHFR gene for use as an amplifiable reporter (e.g., page 33, lines 26-31).

Regarding claim 2, DuBridge teaches the cassette where the promoter/enhancer region comprises a human CMV immediate early 1 promoter and enhancer (e.g., page 28, lines 1-2 and 26-27; page 30, lines 18-20).

Regarding claim 11, DuBridge teaches vectors comprising the integration cassette for site-specific recombination (e.g., page 24, lines 9-11).

Regarding claim 14, DuBridge teaches host cells comprising the vector containing the cassette (e.g., page 44, lines 15-23; page 46, lines 20-22).

Regarding claim 15, DuBridge teaches host cells, which are adapted for growth in suspension and comprise the vector containing the cassette (e.g., page 44, lines 15-23; paragraph bridging pages 45-46; page 46, lines 20-22).

Regarding claim 16, DuBridge teaches host cells, which are adapted for growth in serum free medium and comprise the vector containing the cassette (e.g., page 44, lines 15-23 and 28-30; page 46, lines 20-22).

Regarding claim 17, DuBridge teaches bacterial host cells, such as *E. coli*, comprising the vector containing the cassette (e.g., page 44, lines 15-32; page 45, lines 8-16page 46, lines 7-12). *E. coli* host cells are adapted for growth in suspension in serum free medium.

Regarding claim 18, DuBridge teaches host cells comprising the cassette (e.g., page 44, lines 15-23).

Regarding claim 19, DuBridge teaches host cells, which are adapted for growth in suspension and comprise the cassette (e.g., page 44, lines 15-23; paragraph bridging pages 45-46).

Regarding claim 20, DuBridge teaches host cells, which are adapted for growth in serum free medium and comprise the cassette (e.g., page 44, lines 15-23 and 28-30).

Regarding claim 21, DuBridge teaches bacterial host cells, such as *E. coli*, comprising the cassette (e.g., page 44, lines 15-32; page 45, lines 8-16). *E. coli* host cells are adapted for growth in suspension in serum free medium.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 8 and 11-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perkins et al (US Patent Application Publication No. 2003/0119104, cited as reference AA on the IDS filed 9/5/2007; see the entire reference).

The teachings of Perkins et al are directed to the provision of engineered artificial chromosomes, platform artificial chromosome expression systems ("platform ACes"), that permit tractable, efficient and rational engineering of artificial chromosomes (e.g., paragraphs [0007] and [0008]). Perkins et al teach a recombination system comprising a pair of site-specific recombination sequences and a site-specific recombinase, where the site-specific recombinase catalyzes a recombination reaction between the two site-specific recombination sequences (e.g., paragraphs [0143]-[0144]). Perkins et al teach kits comprising the recombination system (e.g., paragraphs [0013]-[0116] and claim 32). Perkins et al teach the recombination system where the site-specific recombination sequences are FRT sequences, and the recombinase is FLP recombinase (e.g., paragraphs [0145] and [0147]-[0148]). In one embodiment, the first site-specific recombination site is on a platform ACes, and the second site-specific recombination site is on a donor target vector with designed expression cassettes (e.g., paragraphs [0205]-[0207]).

Perkins et al specifically teach the production of ACes in CHO cells (e.g., paragraph [0208]). Thus, Perkins et al teach a CHO host cell comprising a FRT site in the artificial chromosome, which reads on the "host cell comprising an FRT site" of claims 22 and 29, and the CHO cell comprising an FRT site of claim 23. Further, Perkins et al teach the CHO cell comprising the FRT site, where the CHO cells is a CHO-DG44 cell, is adapted for growth in suspension and/or serum-free medium, and/or is dihydrofolate reductase (dhfr)-deficient (e.g., paragraphs [0222] and [0232]), as required by claims 24-28 and 30.

With respect to the donor target vector, Perkins et al teach that the vector comprises a recombination cassette containing a FRT site, a promoterless reporter, and a strong constitutive promoter operably inked to sequence encoding gene products(s) of interest for insertion into the platform artificial chromosome containing the other FRT site (e.g., paragraphs [0038], [0189]-[0197], [0212]-[0215]). An exemplary donor target vector containing an att site in place of a FRT site is depicted in Figure 9. Perkins et al teach the inclusion of a dihydrofolate reductase gene in the donor vector to promote amplification of the target gene in the cell in response to methotrexate treatment (e.g., paragraph [0197]). Perkins et al teach that the gene product of interest encoded by the vector can be a therapeutic product (e.g., paragraph [0015], [0094], [00157] and [0189]). Perkins et al teach that the promoter can be a Fer-1 enhancer/promoter sequence lacking the Iron Response Element (e.g., paragraph [0098]). Perkins et al teach host cells comprising the donor target vector such that site-specific recombination can occur between the artificial chromosome and donor target vector (e.g., paragraph [0214]).

Perkins et al do not explicitly teach that the recombination cassette in the donor target vector comprises a polyA signal domain. Further, Perkins et al do not explicitly teach that the

sequence encoding the gene product of interest is operably linked to the promoter/enhancer region and intron A of a human CMV immediate early 1 (hCMV IE1) gene. Perkins et al do not specifically teach the recombination cassette further comprising a second promoter/enhancer region, a second polynucleotide of interest, and a second polyA signal domain, all operably linked.

Perkins et al teach the commercially available plasmid, pMG (e.g., paragraphs [0314]-[0318]). Plasmid pMG contains two transcriptional units allowing for the coexpression of two heterologous genes from a single vector sequence (e.g., paragraph [0315]). The first transcriptional unit contains a hCMV IE1 enhancer/promoter with intron A located upstream of a multiple cloning site for insertion of a gene of interest, an IRES, the coding sequence for the hygromycin phosphotransferase gene (hph), a polyadenylation signal from a bovine growth hormone gene, and a standard AAUAAA hexanucleotide sequence (e.g., paragraph [0316]). The second transcriptional unit comprises an EF-1α/HTLV hybrid promoter located upstream of a multiple cloning site for insertion of a gene of interest, the Simian Virus 40 (SV40) late polyadenylation signal, and a synthetic AATAAA hexanucleotide sequence (e.g., paragraph [0317]).

With respect to claim 3, Perkins et al teach that the hCMV IE1 enhancer/promoter sequence of pMG is disclosed in SEQ ID NO: 27 (e.g., paragraph [0315]). The sequence taught by Perkins et al is 100% identical to x_1 to x_2 of instant SEQ ID NO: 1, where x_1 is position 139 of SEQ ID NO: 1 and x_2 is position 780 of SEQ ID NO: 1 (see the attached alignment in Appendix I). Claim 3 requires a sequence from about x_1 to about x_2, where x_1 is position 1 to position 70 and x_2 is position 770 to position 780. Given that x_1 itself is variable by 70

nucleotides, a position of about 70 is reasonably considered to be a position up to 140. Thus, Perkins et al teach an hCMV IE1 enhancer/promoter that meets the sequence limitations of claim 3.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the donor target vector comprising the recombination cassette of Perkins et al to include two transcriptional units separated by intervening vector backbone, each unit comprising a promoter/enhancer region, a polynucleotide of interest, and a polyA signal domain, where one of the transcriptional units contains the hCMV IE1 enhancer/promoter with intron A, as taught by Perkins et al. Perkins et al teach that the donor vectors are designed to provide strong constitutive expression of the polynucleotide(s) of interest, and Perkins et al teach transcriptional units comprising a promoter/enhancer, a polynucleotide of interest, and a polyA signal domain, where one of the transcriptional units includes the hCMV IE1 enhancer/promoter with intron A. The hCMV IE1 enhancer/promoter with intron A acts as a strong constitutive promoter. Thus, by using the two transcriptional units in the donor target vector, one would achieve the predictable result of providing donor target vectors for FRT/FLP-mediated recombination with a FRT site in an artificial chromosome within a host cell, such that the proteins encoded by the polynucleotide of interest would be produced. This is a predictable use of prior art elements according to their known functions consistent with the teachings of Perkins et al with regard to the structure of the donor target vector comprising the recombination cassette.

Claims 6 and 7are rejected under 35 U.S.C. 103(a) as being unpatentable over Perkins et al (US Patent Application Publication No. 2003/0119104, cited as reference AA on the IDS filed 9/5/2007; see the entire reference) as applied to claims 1-5, 8 and 11-30 above, and further in view of Thudium et al (US Patent No. 6,893,840 B2; see the entire reference).

The teachings of Perkins et al are described above and applied as before. Further, Perkins et al teach that the hCMV IE1 intron A sequence of pMG is disclosed in SEQ ID NO: 27 (e.g., paragraph [0315]). The sequence taught by Perkins et al contains sequence identical to nucleotides 770-1298 of SEQ ID NO: 1 (see the attached alignment in Appendix II); however, additional sequence is inserted around position 1183 of SEQ ID NO: 1. In other words, the sequence of Perkins et al lacks a deletion between the splice donor site and splice acceptor site of the intron A.

Thus, Perkins et al do not teach the recombination cassette, where intron A of hCMV IE1 comprises a deletion between the splice donor site and splice acceptor site of the intron A and do not teach the intron A sequence from about x_3 to about x_4 of SEQ ID NO: 1, where x_3 is a nucleotide from 770-780 and x_4 is a nucleotide from 1300-1310 of SEQ ID NO: 1.

Thudium et al teach CMV Intron A fragments for use in expression constructs for expressing gene products (e.g., column 1, lines 14-18). Thudium et al teach that intron A is found within the 5'-untranslated region of the hCMV IE1 gene (e.g., paragraph bridging columns 1-2). Thudium et al teach that the use of an intron A fragment is desirable, especially when used in recombinant viral vectors with size constraints for packaging plasmids (e.g., column 2, lines 26-35). Thudium et al teach that by "Intron A fragment" it is meant "a fragment derived from an Intron A sequence of a CMV immediate-early enhancer/promoter region, which does not include

the entire Intron A sequence" (column 5, lines 19-22). The full sequence of CMV IE1 Intron A from hCMV strain Towne is shown as nucleotides 1-820 of SEQ ID NO: 1 (e.g., column 4, lines 1-4; column 5, lines 22-26). However, Thudium et al teach Intron A fragments from any hCMV strain, such as Towne or AD169 (e.g., column 6, lines 40-46). Thudium et al teach that intron A fragments include any internal deletion that retains at least the 5' splice junction sequence (nucleotides 1-7 of SEQ ID NO: 1) and up to 75 or more nucleotides of the Intron A region and at least the 3' splice junction sequence (nucleotides 815-820 of SEQ ID NO: 1) and up to 80 nucleotides or more of the Intron A region (e.g., columns 5-6). Thudium et al specifically teach a series of deletions of Intron A, where 70, 113, 150, 345, 578, 609, 663, 54, 80, 314, 516 and 590 nucleotides are deleted from the intron (e.g., Table 1; Figure3). The deletion present in instant SEQ ID NO: 1 is most similar to the HpaI-MroII deletion shown in Table 1 (see the attached alignment in Appendix III). The CMV promoter/enhancer and HpaI-MroII Intron A fragment provides expression of an operably linked gene (e.g., Figure 4). Thudium et al teach that the hCMV IE1 enhancer/promoter region is one of the strongest enhancer/promoters known and is active in a broad range of cell types (e.g., column 1, lines 53-61). Some deletions, such as the 609 bp NsiI-PvuII deletion (pCON3) provide increased expression of the operably linked gene (e.g., Figure 4; Table I). Further, Thudium et al teach expression cassettes capable of directing the expression of the sequence(s) or gene(s) of interest, comprising the hCMV IE1 promoter/enhancer and Intron A fragment, which is operably linked to the sequence(s) or gene(s) of interest, and a polyadenylation sequence (e.g., column 9, lines 9-27).

With respect to claim 6, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the recombination cassette of Perkins et al to include

an Intron A deletion between the splice donor site and splice acceptor site taught by Thudium et al because Perkins et al teach it is within the ordinary skill in the art to use hCMV IE1 Intron A in a recombination cassette comprising an expression cassette, and Thudium et al teach the use of Intron A fragments in an expression cassette. One would have been motivated to make such a modification in order to receive the expected benefit of providing increased expression by using an Intron A fragment such as the NsiI-PvuII deletion fragment as taught by Thudium et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

With respect to claim 7, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the intron A fragment taught by Perkins et al to include a deletion similar to the HpaI-MroII deletion taught by Thudium et al to result in a sequence identical to nucleotides 770-1298 of instant SEQ ID NO: 1. Thudium et al teach virtually any internal deletion to any hCMV IE1 intron A sequence, as long as the critical residues are present at the 5' splice junction sequence and 3' splice junction sequence. Furthermore, all of the Intron A deletions taught by Thudium et al provided for expression of the heterologous sequence when the Intron A fragment was used with the hCMV IE1 promoter/enhancer. Thus, one would expect any Intron A fragment to be capable of supporting expression of a heterologous sequence, as long as the 5' splice junction sequence and 3' splice junction sequences are present. Because Perkins et al teach the use of viral vectors comprising the recombination cassette, one would have been motivated to make such a deletion in order to receive the expected benefit of reducing the size of the regulatory sequence when dealing with

viral vectors that have size limits for packaging. Moreover, both Perkins et al and Thudium et al teach the use of hCMV IE1 Intron A sequence in expression cassettes, and it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute on intron A fragment for another to achieve the predictable result of providing expression of an operably linked sequence. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perkins et al (US Patent Application Publication No. 2003/0119104, cited as reference AA on the IDS filed 9/5/2007; see the entire reference) as applied to claims 1-5, 8 and 11-30 above, and further in view of Alvarez et al (US Patent Application Publication No. 2003/0215913 A1; see the entire reference) in view of GenBank Accession No. K00470 (GI: 183174, October 1999; see the entire reference).

The teachings of Perkins et al are described above and applied as before. As described above, Perkins et al teach a transcription unit comprising a bovine growth hormone 3' untranslated region and polyA signal.

Perkins et al do not teach a transcription unit in the recombination cassette where the polyA signal domain comprises SEQ ID NO: 3.

Alvarez et al teach a plasmid for expressing a gene of interest under the strong promoter of the long terminal repeat (LTR) of the Rous Sarcoma Virus plus a fragment isolated from the enhancer of the immediate early gene of human cytomegalovirus (CMV), where the vector

further comprises a multiple cloning site to allow insertion of a gene of interest, and a polyadenylation site from the human growth hormone gene (e.g., paragraph [0245]. Alvarez et al teach that this vector is for cloning and expression in CHO cells (e.g., title above paragraph [0244]).

GenBank Accession No. K00470 teaches the sequence of the human growth hormone gene, including the polyA signal. GenBank Accession No. K00470 teaches the sequence of instant SEQ ID NO: 3 (see the attached alignment in Appendix IV).

Because Perkins et al and Alvarez et al teach the use of a growth hormone 3' untranslated region and polyA signal for expression of a sequence of interest in CHO cells, it would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the bovine growth hormone 3' untranslated region and polyA signal of Perkins et al with the human growth hormone 3' untranslated region and polyA signal of Alvarez et al. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the sequence of GenBank Accession No. K00470 as the 3' untranslated region and polyA signal of human growth hormone, because Alvarez et al do not teach the specific nucleotide sequence. One would have looked to the known human growth hormone 3' untranslated region and polyA signal sequences in order to provide the actual sequence for constructing the vector. Thus, it would have been obvious to use the known sequence of GenBank Accession No. K00470. It would have been obvious to one skilled in the art to substitute the human sequence for the bovine sequence to achieve the predictable result of providing a polyA signal for expression of the sequence of interest in CHO cells.

Claims 1-30 are rejected under 35 U.S.C. 103(a) as being obvious over Sisk et al (US Patent No. 7,494,805 B2; see the entire reference) in view of Perkins et al (US Patent Application Publication No. 2003/0119104, cited as reference AA on the IDS filed 9/5/2007; see the entire reference).

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Sisk et al teach an expression cassette that includes an operably linked human CMV immediate early 1 (hCMV IE1) promoter/enhancer region, a variable length intervening sequence (VLIVS) comprising a splice donor site and a splice acceptor site, a polynucleotide of interest, and a variant human growth hormone (hGHv) polyA signal domain, which is at least 100 nucleotides in length and contains the sequence AATAAA (e.g., column 1, line 29 to

column 2, line 6; paragraph bridging columns 3-4). Sisk et al teach the cassette further comprising a dihydrofolate reductase (dhfr) gene operably linked to a SV40 promoter/enhancer element and a SV40 polyadenylation region (e.g., column 6, lines 20-31). Further, Sisk et al teach a vector comprising the expression cassette and host cells comprising the vector (e.g., column 1, lines 51-54 column 5, lines 12-27). Sisk et al teach a hCMV IE1 promoter/enhancer region 100% identical to nucleotides 5-780 of SEQ ID NO: 1 (see the attached alignment in Appendix V; note that Sisk et alt each that SEQ ID NO: 1 is a circular DNA molecule (e.g., column 5, lines 12-27)). Sisk et al teach the expression cassette where the VLIVS is from intron A of CMV, or a fragment thereof (e.g., column 3, lines 57-64; column 4, lines 29-41). Sisk et al teach the VLVS of nucleotides 770-1304 of SEQ ID NO: 1 (see the attached alignment in Appendix VI). Sisk et al teach that the sequence of the hGHv 3' untranslated region is from GenBank Accession No. K00470 and is shown in SEQ ID NO: 18 (e.g., column 4, lines 51-54). The sequence of SEQ ID NO: 18 taught by Sisk et al is 100% identical to instant SEQ ID NO: 3 (see the attached alignment in Appendix VII). Sisk et al teach that the vector of the invention may include additional promoter/enhancer elements and polyA signal domains flanking a selectable marker or polynucleotide of interest; the addition of the further elements would result in vector backbone sequence separating the first and second expression units (e.g., column 6, lines 14-20; Figures). Sisk et al teach that the polynucleotide of interest may encode a therapeutic product (e.g., column 9, lines 48-51). With respect to the host cells comprising the vector containing the expression cassette, Sisk et la teach that they host cells may be a CHO cell, a CHO-DG44, a cell adapted for growth in suspension, or a dhfr-deficient CHO cell (e.g., column 12, line 26 to column 13, line 12). A kit is a collection of items, and Sisk et al teach a

collection of items including the expression cassette, vector comprising the expression cassette and CHO cells.

Sisk et al do not teach the expression cassette comprising a FRT recombination domain and do not teach the CHO cell comprising a FRT site. Sisk et al do not teach the host cells adapted for growth in serum free medium.

The teachings of Perkins et al are directed to the provision of engineered artificial chromosomes, platform artificial chromosome expression systems ("platform ACes"), that permit tractable, efficient and rational engineering of artificial chromosomes (e.g., paragraphs [0007] and [0008]). Perkins et al teach a recombination system comprising a pair of site-specific recombination sequences and a site-specific recombinase, where the site-specific recombinase catalyzes a recombination reaction between the two site-specific recombination sequences (e.g., paragraphs [0143]-[0144]). Perkins et al teach kits comprising the recombination system (e.g., paragraphs [0013]-[0116] and claim 32). Perkins et al teach the recombination system where the site-specific recombination sequences are FRT sequences, and the recombinase is FLP recombinase (e.g., paragraphs [0145] and [0147]-[0148]). In one embodiment, the first site-specific recombination site is on a platform ACes, and the second site-specific recombination site is on a donor target vector with designed expression cassettes (e.g., paragraphs [0205]-[0207]).

Perkins et al specifically teach the production of ACes in CHO cells (e.g., paragraph [0208]). Thus, Perkins et al teach a CHO host cell comprising a FRT site in the artificial chromosome, which reads on the "host cell comprising an FRT site" of claims 22 and 29, the CHO cell comprising an FRT site of claim 23. Further, Perkins et al teach the CHO cell comprising the FRT site, where the CHO cells is a CHO-DG44 cell, is adapted for growth in

suspension and/or serum-free medium, and/or is dihydrofolate reductase (dhfr)-deficient (e.g., paragraphs [0222] and [0232]), as required by claims 24-28 and 30).

With respect to the donor target vector, Perkins et al teach that the vector comprises a recombination cassette containing a FRT, a promoterless reporter, and a strong constitutive promoter operably inked to sequence encoding gene products(s) of interest for insertion into the platform artificial chromosome containing the other FRT site (e.g., paragraphs [0038], [0189]-[0197], [0212]-[0215]). An exemplary donor target vector containing an att site in place of a FRT site is depicted in Figure 9. Perkins et al teach the inclusion of a dihydrofolate reductase gene in the donor vector to promote amplification of the target gene in the cell in response to methotrexate treatment (e.g., paragraph [0197]). Perkins et al teach that the gene product of interest encoded by the vector can be a therapeutic product (e.g., paragraph [0015], [0094], [00157] and [0189]). Perkins et al teach that the promoter can be a Fer-1 enhancer/promoter sequence lacking the Iron Response Element (e.g., paragraph [0098]). Perkins et al teach host cells comprising the donor target vector such that site-specific recombination can occur between the artificial chromosome and donor target vector (e.g., paragraph [0214]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the expression cassettes, vectors and host cells of Sisk et al to include the FRT sites taught by Perkins et al because Perkins et al teach it is within the ordinary skill in the art to use expression cassettes further comprising a FRT site and Sisk et al teach expression cassettes. Further, Sisk et al teach the introduction of the expression cassettes and vectors into CHO cells, and Perkins et al teach CHO cells comprising a FRT site. Moreover, Perkins et al teach the CHO cells adapted for growth in serum-free medium.

One would have been motivated to make such a modification in order to receive the expected benefit of providing vectors and platform artificial chromosomes in CHO cells, which permit tractable, efficient and rational engineering as taught by Perkins et al. Using cells adapted to grow in a serum-free medium would allow the cells to be used in the production of proteins without the presence of serum, resulting in the expected benefit of simplified purification of the protein of interest. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9 and 11-30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3, 17-19, 29-31, 38, 42 and 44 of U.S. Patent No.

7,494,805 (hereinafter the '805 patent) in view of Perkins et al (US Patent Application Publication No. 2003/0119104, cited as reference AA on the IDS filed 9/5/2007; see the entire reference).

Both sets of claims are directed to a cassette comprising a promoter/enhancer region, a polynucleotide of interest, and a polyA signal domain and a dhfr polynucleotide. Instant claim 1 requires a promoter/enhancer region, a polynucleotide of interest, a polyA signal domain, an FRT recombination domain, and a dhfr polynucleotide. Instant claim 2 limits the promoter/enhancer region to a human CMV immediate early 1 (hCMV IE1) promoter/enhancer region. Instant claim 4 further requires a variable length intervening sequence (VLIVS) comprising a splice donor and splice acceptor site. Instant claim 5 limits the VLIVS to an intron A of an hCMV IE1 gene. Claims 17 and 18 of the '805 patent are directed to a cassette comprising an hCMV IE1 promoter/enhancer region, a polynucleotide of interest, a variant human growth hormone (hGHv) poly A signal domain of at least 100 nucleotides in length and 92% identical to a wild-type human growth hormone polyA signal domain, a VLIVS comprising a splice donor and splice acceptor site on an intron A of hCMV IE1, and a dhfr polynucleotide. The hGHv polyA signal domain of the '805 patent is 100% identical to instant SEQ ID NO: 3 (see the attached alignment in Appendix VII). Further, the vectors of claims 38, 42 and 44 comprise an hCMV IE1 promoter/enhancer, a polynucleotide of interest, an hGHv polyA, and a dhfr polynucleotide. Thus, claims 17, 18, 38, 42 and 44 of the '805 patent are narrower in scope than instant claims 1, 2, 4, 5, 9 and 11, except Sisk et al do not teach the cassette comprising the FRT site. Further, the vector of claim 38 includes intron A of hCMV IE1. Thus, claim 38 of the

'805 patent is narrower in scope than instant claim 5 except that it does not include an FRT recombination domain.

Although, the claims of the '805 patent do not recite an FRT recombination domain or the particulars of the host cell, the prior art teaches these limitations. The teachings of Perkins et al are directed to the provision of engineered artificial chromosomes, platform artificial chromosome expression systems ("platform ACes"), that permit tractable, efficient and rational engineering of artificial chromosomes (e.g., paragraphs [0007] and [0008]). Perkins et al teach a recombination system comprising a pair of site-specific recombination sequences and a site-specific recombinase, where the site-specific recombinase catalyzes a recombination reaction between the two site-specific recombination sequences (e.g., paragraphs [0143]-[0144]). Perkins et al teach kits comprising the recombination system (e.g., paragraphs [0013]-[0116] and claim 32). Perkins et al teach the recombination system where the site-specific recombination sequences are FRT sequences, and the recombinase is FLP recombinase (e.g., paragraphs [0145] and [0147]-[0148]). In one embodiment, the first site-specific recombination site is on a platform ACes, and the second site-specific recombination site is on a donor target vector with designed expression cassettes (e.g., paragraphs [0205]-[0207]).

Perkins et al specifically teach the production of ACes in CHO cells (e.g., paragraph [0208]). Thus, Perkins et al teach a CHO host cell comprising a FRT site in the artificial chromosome, which reads on the "host cell comprising an FRT site" of claims 22 and 29, the CHO cell comprising an FRT site of claim 23. Further, Perkins et al teach the CHO cell comprising the FRT site, where the CHO cells is a CHO-DG44 cell, is adapted for growth in suspension and/or serum-free medium, and/or is dihydrofolate reductase (dhfr)-deficient (e.g.,

paragraphs [0222] and [0232]), as required by claims 24-28 and 30). With respect to the donor target vector, Perkins et al teach that the vector comprises a recombination cassette containing a FRT, a promoterless reporter, and a strong constitutive promoter operably inked to sequence encoding gene products(s) of interest for insertion into the platform artificial chromosome containing the other FRT site (e.g., paragraphs [0038], [0189]-[0197], [0212]-[0215]). Perkins et al teach host cells comprising the donor target vector such that site-specific recombination can occur between the artificial chromosome and donor target vector (e.g., paragraph [0214]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the expression cassettes, vectors and host cells of Sisk et al to include the FRT sites taught by Perkins et al because Perkins et al teach it is within the ordinary skill in the art to use expression cassettes further comprising a FRT site and the '805 patent claims expression cassettes. One would have been motivated to make such a modification in order to receive the expected benefit of providing vectors and platform artificial chromosomes in CHO cells, which permit tractable, efficient and rational engineering as taught by Perkins et al. Using cells adapted to grow in a serum-free medium would allow the cells to be used in the production of proteins without the presence of serum, resulting in the expected benefit of simplified purification of the protein of interest.

Looking at the claims of the '805 patent, obvious variants of the cassettes include the sequence of SEQ ID NO: 1 (claim 3), polynucleotide of interest encoding a therapeutic agent (claim 19), an expression vector comprising the cassette (claim 29), and a host cell comprising the vector or cassette (claims 30 and 31). Thus, the conflicting claims are not patentably distinct from instant claims 3, 6-8, 14 and 18.

Accordingly, instant claims 1-9 and 11-30 are not patentably distinct from claims 3, 17-19, 29-31, 38, 42 and 44 of the '805 patent. Thus, the instant claims, if allowed, would extend patent protection of the '805 invention. Further, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the rights to the '805 invention, then two different assignees would hold patent claims to the claimed invention.

Claims 1-5, 8, 9, 11 and 14-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15, 16, 21-23, 28, 29, 31 and 32 of copending Application No. 12/349,899 (hereinafter the '899 application) in view of Perkins et al (US Patent Application Publication No. 2003/0119104, cited as reference AA on the IDS filed 9/5/2007; see the entire reference).

Both sets of claims are directed to a cassette comprising a promoter/enhancer region, a polynucleotide of interest, and a polyA signal domain and a dhfr polynucleotide. Instant claim 1 requires a promoter/enhancer region, a polynucleotide of interest, a polyA signal domain, an FRT recombination domain, and a dhfr polynucleotide. Instant claim 2 limits the promoter/enhancer region to a human CMV immediate early 1 (hCMV IE1) promoter/enhancer region. Instant claim 4 further requires a variable length intervening sequence (VLIVS) comprising a splice donor and splice acceptor site. Claims 21 and 22 of the '899 application are directed to a cassette comprising an hCMV IE1 promoter/enhancer region, a polynucleotide of interest, a polyA signal domain comprising SEQ ID NO: 19, and a dhfr polynucleotide. The polyA signal domain of SEQ ID NO: 19 of the '899 application is identical to at least 100 nucleotides of instant SEQ ID NO: 3 (see the attached alignment in Appendix VIII). Thus,

claims 21 and 22 of the '899 application are narrower in scope than instant claims 1, 2 and 9 except the '899 application does not claim the cassette comprising the FRT site.

Although, the claims of the '899 application do not recite an FRT recombination domain or the particulars of the host cell, the prior art teaches these limitations. The teachings of Perkins et al are directed to the provision of engineered artificial chromosomes, platform artificial chromosome expression systems ("platform ACes"), that permit tractable, efficient and rational engineering of artificial chromosomes (e.g., paragraphs [0007] and [0008]). Perkins et al teach a recombination system comprising a pair of site-specific recombination sequences and a site-specific recombinase, where the site-specific recombinase catalyzes a recombination reaction between the two site-specific recombination sequences (e.g., paragraphs [0143]-[0144]). Perkins et al teach kits comprising the recombination system (e.g., paragraphs [0013]-[0116] and claim 32). Perkins et al teach the recombination system where the site-specific recombination sequences are FRT sequences, and the recombinase is FLP recombinase (e.g., paragraphs [0145] and [0147]-[0148]). In one embodiment, the first site-specific recombination site is on a platform ACes, and the second site-specific recombination site is on a donor target vector with designed expression cassettes (e.g., paragraphs [0205]-[0207]).

Perkins et al specifically teach the production of ACes in CHO cells (e.g., paragraph [0208]). Thus, Perkins et al teach a CHO host cell comprising a FRT site in the artificial chromosome, which reads on the "host cell comprising an FRT site" of claims 22 and 29, the CHO cell comprising an FRT site of claim 23. Further, Perkins et al teach the CHO cell comprising the FRT site, where the CHO cells is a CHO-DG44 cell, is adapted for growth in suspension and/or serum-free medium, and/or is dihydrofolate reductase (dhfr)-deficient (e.g.,

paragraphs [0222] and [0232]), as required by claims 24-28 and 30). With respect to the donor target vector, Perkins et al teach that the vector comprises a recombination cassette containing a FRT, a promoterless reporter, and a strong constitutive promoter operably inked to sequence encoding gene products(s) of interest for insertion into the platform artificial chromosome containing the other FRT site (e.g., paragraphs [0038], [0189]-[0197], [0212]-[0215]). Perkins et al teach host cells comprising the donor target vector such that site-specific recombination can occur between the artificial chromosome and donor target vector (e.g., paragraph [0214]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the expression cassettes, vectors and host cells of Sisk et al to include the FRT sites taught by Perkins et al because Perkins et al teach it is within the ordinary skill in the art to use expression cassettes further comprising a FRT site and the '899 application claims expression cassettes. One would have been motivated to make such a modification in order to receive the expected benefit of providing vectors and platform artificial chromosomes in CHO cells, which permit tractable, efficient and rational engineering as taught by Perkins et al.

Looking at the claims of the '899 application, obvious variants of the cassettes include a variable length intervening sequence (VLVIS) comprising a splice donor and splice acceptor site, where the VLIVS comprises an intron A of a hCMV IE1 gene (claims 15 and 16) the polynucleotide of interest encoding a therapeutic agent (claims 23, 28 and 29), an expression vector comprising the cassette (claim 31), and a host cell comprising the vector or cassette (claim 32). Thus, instant claims 4, 5, 8, 11, 14 and 18 are not patentably distinct from the conflicting claims.

This is a provisional obviousness-type double patenting rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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